Cu(I)-CATALYZED COUPLING OF (9-BENZYLPURIN-6-YL)MAGNESIUM CHLORIDE WITH ALLYL HALIDES: AN APPROACH TO 6-ALLYLPURINE DERIVATIVES

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Dedicated to Professor Antonín Holý on the occasion of his 70th birthday.

6-Allylpurine derivatives are formed by Cu(I)-catalyzed coupling of (9-benzyl-9*H*-purin-6-yl)-magnesium chloride with allyl halides. The reaction is accompanied by allylic rearrangement in some cases. Under acid conditions the double bond of the allyl group rearranges to the conjugation with purine ring.
Keywords: Purines; Cross-coupling reactions; Palladium; Grignard reagent; Copper; Allylic rearrangement.

Many structurally modified purine derivatives are biologically active[1]. Their activities span a wide range from antiviral[2] to antineoplastic and antileukemic[3]. Some substituted purines are inhibitors of cyclin-dependent kinases[4] with potential application in a large variety of pathologies such as cancers, glomerulonephritis, restenosis, proliferation of parasites, and neurodegenerative disorders[5]. Substituted purines also attract attention as inhibitors of estrogen sulfotransferase[6], tubulin polymerization[7] and as antagonists of a corticotropin-releasing hormone[8].

Introduction of carbon substituents bearing double C=C bond brings a possibility of further modification of the side chain and, thus, it enhances the chance of the interaction with receptors. 2-, 6- or 8-alkenylpurines can be easily prepared by transition metal-catalyzed cross-coupling reactions of alkenylstananes, alkenylboronic acids, alkenylzinc and organocooper reagents with appropriate halopurines[9]. The above mentioned cross-coupling reactions work best with sp² and sp halides, however, examples of success-

ful introduction of alkyl groups e.g. by Negishi and Stille coupling[10] have been published.

On contrary to alkenylpurines, there are only two examples of the introduction of allyl group to the position 8 (ref.[11]) and 2 (ref.[12]) of purine ring using Stille coupling and to the best of our knowledge, the allylation of the position 6 has not been reported yet. We attempted to prepare 6-allylpurines by the reaction of allylcopper reagents with 6-chloropurine derivatives[13] and by the reaction of 2-chloro-6-iodopurines with allyl Grignard reagents[14]. However, the reaction of allyl organometallic reagent to position 8 of the purine ring was observed in both cases.

The opposite approach to the above-discussed cross-coupling reactions – coupling of metalated purines with electrophiles – can, in principle, be used for the preparation of C-substituted purines. However, in spite of the lithiated and zincated purines are known, the chemistry of 6- and 2-lithiated purines suffers from easy (–80 °C) rearrangement to the more stable 8-lithiated derivatives. Therefore these reactions have to be done at –130 °C or the position 8 needs to be protected[15]. Purines zincated at the position 6 have been prepared, but only their Pd-catalyzed cross-coupling reaction with arylhalides has been reported[16]. Recently we published the preparation of magnesylated purines and their reaction with electrophiles[17]. This approach brings an opportunity to obtain 6-allylpurines by coupling of magnesylated purines with allyl halides. Here we wish to report our results.

Reaction of (9-benzylpurin-6-yl)magnesium chloride (**1**), prepared by the exchange reaction of 9-benzyl-6-iodopurine (**2**) with *i*-PrMgCl [11], with 3-chloro-2-methylprop-1-ene (**3a**) was chosen as a model reaction. While no productive reaction was observed without additives, the reaction in the presence of Cu(I) salts afforded the desired product **4a**. After brief optimization of reaction conditions it was found that CuI is superior to CuCN. The best result (80% HPLC yield) was obtained using 20 mole % of CuI (Scheme 1, Table I).
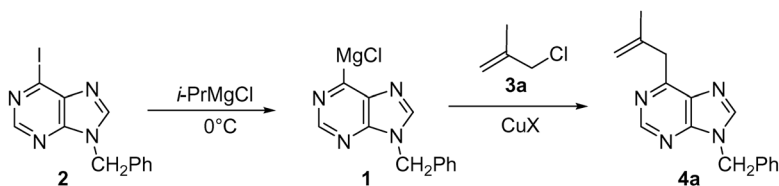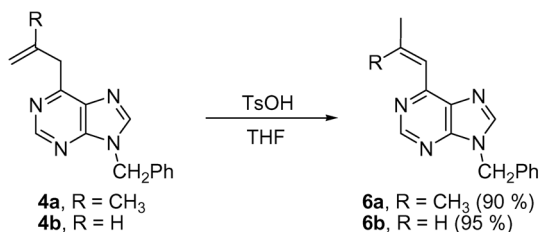

SCHEME 1

TABLE I
Optimization of reaction conditions for the coupling of **1** with **3a**

Additive (mole %)	Reaction conditions	HPLC yield, %
None	0 °C to r.t., overnight	0
CuCN (20)	0 °C to r.t., overnight	65
CuCN (100)	0 °C to r.t., overnight	trace
CuCN (10)	0 °C to r.t., overnight	60
CuI (20)	–80 °C to r.t.	80
CuI (10)	–80 °C to r.t.	28

The optimal conditions were used for the reaction of **1** with other substrates than **3a** (Table II). Similar results were obtained with allyl bromide (**3b**) and 3-bromocyclohexane (**3c**) (Table II, entries 2, 3). Reaction of 1-chlorobut-2-ene (**3d**) was accompanied by allylic rearrangement giving a mixture of unrearranged **4d$_1$** and rearranged **4d$_2$** products in ca. 3:2 ratio (Table II, entry 4). Reaction with 1-chloro-3-methylbut-2-ene (**3e**) and 1-chloro-3-phenylprop-1-ene (**3f**) afforded only low yields of coupled products (Table II, entries 5, 6). Application of this methodology to a functionalized allyl derivative – (*E*)-1-acetoxy-4-chlorobut-2-ene (**3g**) – led to a low yield of the coupled product **4g** accompanied by the product of elimination of the acetoxy group, diene **5** (Table II, entry 7).
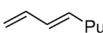
Upon prolonged staying in solution or even in substance, the double bond of the obtained 6-allylpurine derivatives rearranges to the conjugation with purine ring. The rearrangement is acid-catalyzed and can be avoided by washing the solution after chromatographic separation of **4** with aqueous solution of K$_2$CO$_3$. In the presence of a catalytic amount of 4-methylbenzene-1-sulfonic acid the allylpurines with terminal double bonds (**4a**, **4b**) rearrange quantitatively and the corresponding conjugated derivatives **6a** and **6b** can be isolated in almost quantitative yield (Scheme 2). With the

4a, R = CH$_3$
4b, R = H

6a, R = CH$_3$ (90 %)
6b, R = H (95 %)

SCHEME 2

other 6-allylpurines the attempts of acid-catalyzed isomerization resulted in partial decomposition and formation of complex, inseparable mixtures of unidentified products. This instability is in accordance with the reported high reactivity of multiple bonds in conjugation with purine ring, which are prone to addition of nucleophiles[18].

TABLE II
Reaction of magnesylated purine **1** with allyl halides[a] (Pu = 9-benzylpurin-6-yl)

Entry	Allyl halide	Product (yield %)[b]
1	**3a**	**4a** (54)
2	**3b**	**4b** (53)
3	**3c**	**4c** (51)
4	**3d**	**4d₁** (27) **4d₂** (19)
5	**3e**	**4e** (30)
6	**3f**	**4f** (20)
7	**3g**	**4g** (7) **5** (10)

[a] Reaction conditions: THF, –78 °C to room temperature. [b] Isolated yield.

In conclusion, 6-allylpurines can be easily prepared by the reaction of purine-6-ylmagnesium chloride with allyl halides. In some cases the reaction is accompanied by allylic rearrangement. The obtained 6-allylpurines are acid-sensitive and easily rearrange to the compounds with the double bond in conjugation with the purine ring, or they decompose.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra (δ, ppm; J, Hz) were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz) and Bruker DRX 500 Avance (^{1}H, 500.13 MHz; ^{13}C, 125.77 MHz) spectrometers at 298 K. Unambiguous assignment of NMR signals is based on ^{13}C{^{1}H}, ^{13}C APT, COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC spectra. IR spectra (wavenumbers in cm^{-1}) were recorded on Nicolet 750 FT-IR. Mass spectra were measured on an Autospec Ultima (Micromass) spectrometer. The solvents were dried and degassed by standard procedures. Silica gel (ICN SiliTech, 32-63) was used for column chromatography. 9-Benzyl-6-iodopurine (**1**) was prepared by the reported procedure[10].

General Method for the Preparation of Allylpurines 4a–4g

To the ice-cooled solution of 9-benzyl-6-iodopurine (400 mg, 1.19 mmol) in THF (12 ml), *i*-PrMgCl (0.70 ml, 1.4 mmol) of 2 M solution in diethyl ether was added via syringe and the solution was stirred at this temperature for 15 min. The obtained solution of the Grignard reagent was slowly added to a suspension of CuI (54 mg, 0.28 mmol) in THF (32 ml) precooled to –78 °C. The mixture was then allowed to warm to 0 °C, stirred at that temperature for 15 min and then again cooled to –78 °C. An allyl halide (1.8 mmol) was then added, the reaction mixture was allowed to warm at room temperature and stirred for another 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride (20 ml) and concentrated ammonia (6 ml). The mixture was stirred for 30 min and extracted with diethyl ether (3 × 30 ml). Combined extracts were dried over anhydrous MgSO$_4$, solvents were evaporated in vacuum and the residue chromatographed on silica (32 g) in a hexane/ethyl acetate mixture (1:2). The collected fractions containing the product were washed with saturated aqueous Na$_2$CO$_3$ (20 ml), the aqueous phase was washed with diethyl ether (3 × 30 ml) and dried over K$_2$CO$_3$. The yields of the obtained allylpurines **4a–4g** are in Table II.

9-Benzyl-6-(2-methylprop-2-en-1-yl)-9H-purine (**4a**). M.p. 44–46 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 1.81 (s, 3 H, CH$_3$); 3.95 (s, 2 H, CH$_2$-Pu); 4.87 (s, 1 H, =CH$_2$); 4.94 (s, 1 H, =CH$_2$); 5.44 (s, 2 H, CH$_2$-Ph); 7.25–7.35 (m, 5 H, Ph); 8.02 (s, 1 H, H-8 Pu); 8.96 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 22.6 (CH$_3$), 41.3 (CH$_2$-Pu), 47.2 (CH$_2$-Ph), 113.5 (C=**C**H$_2$), 127.8 (CH Ph), 128.5 (CH Ph), 129.0 (CH Ph), 132.8 (C), 134.9 (C), 141.8 (**C**=CH$_2$), 143.8 (C-8 Pu), 150.9 (C), 152.6 (C-2 Pu), 160.0 (C). IR (CHCl$_3$): 2988, 1594, 1500, 1457, 1406, 1334. HR-MS: calculated for C$_{16}$H$_{16}$N$_4$ 264.1375, found 264.1371.

6-Allyl-9-benzyl-9H-purine (**4b**). M.p. 48–50 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 3.98–4.02 (m, 2 H, CH$_2$-Pu); 5.18–5.23 (m, 1 H, CH=C**H**$_2$); 5.26–5.33 (m, 1 H, CH=C**H**$_2$); 5.44 (s, 2 H, CH$_2$-Ph); 6.15–6.28 (m, 1 H, C**H**=CH$_2$); 7.28–7.38 (m, 5 H, Ph); 8.02 (s, 1 H, H-8 Pu); 8.94 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 37.5 (CH$_2$-Pu), 47.1 (CH$_2$-Ph), 117.6 (CH=**C**H$_2$),

127.7 (CH Ph), 128.4 (CH Ph), 129.0 (CH Ph), 132.1 (C), 133.4 (**C**H=CH$_2$), 135.0 (C), 143.6 (C-8 Pu), 150.9 (C), 152.6 (C-2 Pu), 160.1 (C). IR (CHCl$_3$): 2990, 1596, 1499, 1457, 1406, 1333. HR-MS: calculated for C$_{15}$H$_{14}$N$_4$ 250.1218, found 250.1217.

9-Benzyl-6-(cyclohex-2-en-1-yl)-9H-purine (**4c**). M.p. 67–69 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 1.62–2.24 (m, 6 H, CH$_2$); 4.34 (m, 1 H, CH-Pu); 5.44 (s, 2 H, CH$_2$-Ph); 5.87–5.91 (m, 1 H, C**H**=CH); 6.01–6.07 (m, 1 H, CH=C**H**); 7.31–7.38 (m, 5 H, Ph); 8.01 (s, 1 H, H-8 Pu); 8.97 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 21.6 (CH$_2$), 24.7 (CH$_2$), 29.1 (CH$_2$), 39.2 (CH-Pu), 47.2 (CH$_2$-Ph), 126.9 (CH), 127.8 (CH Ph), 128.5 (CH Ph), 129.0 (CH Ph), 129.2 (CH), 131.8 (C), 135.1 (C), 143.4 (C-8 Pu), 150.9 (C), 152.8 (C-2 Pu), 165.4 (C). IR (CHCl$_3$): 2988, 2941, 1591, 1500, 1456, 1406, 1333. HR-MS: calculated for C$_{18}$H$_{18}$N$_4$ 290.1531, found 290.1541.

(E)-9-Benzyl-6-(but-2-en-1-yl)-9H-purine (**4d$_1$**). M.p. 46–48 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 1.69 (dd, *J* = 6.0, 1.0, 3 H, CH$_3$); 3.92 (d, *J* = 6.2, 2 H, CH$_2$-Pu); 5.43 (s, 2 H, CH$_2$-Ph); 5.64–5.94 (m, 2 H, C**H**=CH); 7.29–7.36 (m, 5 H, Ph); 8.01 (s, 1 H, H-8 Pu); 8.93 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 18.0 (CH$_3$), 36.4 (CH$_2$-Pu), 47.2 (CH$_2$-Ph), 125.9 (CH), 127.8 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 132.1 (C), 135.1 (C), 143.7 (C-8 Pu), 150.9 (C), 152.7 (C-2 Pu), 161.0 (C). IR (CHCl$_3$): 2920, 1595, 1500, 1456, 1406, 1333. HR-MS: calculated for C$_{16}$H$_{16}$N$_4$ 264.1375, found 264.1370.

9-Benzyl-6-(1-methylprop-2-en-1-yl)-9H-purine (**4d$_2$**). M.p. 38–40 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 1.57 (d, *J* = 7.2, 3 H, CH$_3$); 4.32–4.41 (m, 1 H, CH-Pu); 5.11–5.15 (m, 1 H, CH=C**H**$_2$); 5.20–5.27 (m, 1 H, CH=C**H**$_2$); 5.43 (s, 2 H, CH$_2$-Ph); 6.28 (ddd, *J* = 7.4, 10.2, 17.3, 1 H, C**H**=CH$_2$); 7.29–7.37 (m, 5 H, Ph); 8.00 (s, 1 H, H-8 Pu); 8.95 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 19.1 (CH$_3$), 41.3 (CH-Pu), 47.3 (CH$_2$-Ph), 115.1 (CH=**C**H$_2$), 127.9 (CH), 128.6 (CH), 129.1 (CH), 131.5 (C), 135.1 (C), 140.1 (**C**H=CH$_2$), 143.5 (C-8 Pu), 151.1 (C), 152.8 (C-2 Pu), 164.2 (C). IR (CHCl$_3$): 2936, 1590, 1500, 1457, 1406, 1332. HR-MS: calculated for C$_{16}$H$_{16}$N$_4$ 264.1375, found 264.1371.

9-Benzyl-6-(3-methylbut-2-en-1-yl)-9H-purine (**4e**). M.p. 56–58 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 1.75 (s, 3 H, CH$_3$); 1.81 (s, 3 H, CH$_3$); 3.95 (d, *J* = 6.9, 2 H, CH$_2$-Pu); 5.43 (s, 2 H, CH$_2$-Ph); 5.56–5.60 (m, 1 H, CH); 7.26–7.37 (m, 5 H, Ph); 8.00 (s, 1 H, H-8 Pu); 8.93 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 18.1 (CH$_3$), 25.7 (CH$_3$), 32.1 (CH$_2$-Pu), 47.2 (CH$_2$-Ph), 119.0 (**C**H=C), 127.8 (CH Ph), 128.5 (CH Ph), 129.1 (CH Ph), 132.1 (C), 134.7 (CH=**C**), 135.1 (C), 143.5 (C-8 Pu), 150.8 (C), 152.7 (C-2 Pu), 161.7 (C). IR (CHCl$_3$): 2988, 1595, 1499, 1456, 1406, 1333. HR-MS: calculated for C$_{17}$H$_{18}$N$_4$ 278.1531, found 278.1537.

(E)-9-Benzyl-6-(3-phenylprop-2-en-1-yl)-9H-purine (**4f**). Oil. ^{1}H NMR (CDCl$_3$, 500 MHz): 4.15 (d, *J* = 6.5, 2 H, CH$_2$-Pu); 5.45 (s, 2 H, CH$_2$-Ph); 6.58–6.73 (m, 2 H, C**H**=CH); 7.14–7.40 (m, 10 H, Ph); 8.04 (s, 1 H, H-8 Pu); 8.96 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 125 MHz): 36.9 (CH$_2$-Pu), 47.3 (CH$_2$-Ph), 125.2 (CH=), 126.5 (CH Ph), 127.5 (CH Ph), 128.1 (CH Ph), 128.7 (CH Ph), 128.8 (CH Ph), 129.4 (CH Ph), 132.3 (C-5 Pu), 133.0 (CH=), 135.3 (C Ph), 137.4 (C Ph), 144.1 (C-8 Pu), 151.3 (C-4 Pu), 153.0 (C-2 Pu), 160.6 (C-6 Pu). IR (CHCl$_3$): 1595, 1499, 1455, 1406, 1333. HR-MS: calculated for C$_{21}$H$_{18}$N$_4$ 326.1531, found 326.1527.

2-(9-Benzyl-9H-purin-6-yl)but-3-en-1-yl acetate (**4g**). Oil. ^{1}H NMR (CDCl$_3$, 500 MHz): 1.94 (s, 3 H, CH$_3$C=O); 4.57–4.60 (m, 1 H, C**H**-CH$_2$-O); 4.66 (dd, *J* = 7.3, 2.6, 2 H, CH$_2$-OAc); 5.24 (d, *J* = 10.2, 1 H, =CHH$_{cis}$); 5.33 (d, *J* = 17.2, 1 H, =CHH$_{trans}$); 5.45 (s, 2 H, CH$_2$-Ph); 6.20 (m, 1 H, C**H**=CH$_2$); 7.29–7.39 (m, 5 H, Ph); 8.03 (s, 1 H, H-8 Pu); 8.97 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 125 MHz): 20.8 (**C**H$_3$C=O), 46.7 (**C**H-Pu), 47.3 (CH$_2$-Ph), 65.4 (CH$_2$-OAc), 118.6

(=CH$_2$), 128.0 (CH Ph), 128.7 (CH Ph), 129.2 (CH Ph), 132.3 (C-5 Pu), 134.9 (**C**H=CH$_2$), 135.0 (C Ph), 144.0 (C-8 Pu), 151.3 (C-4 Pu), 152.7 (C-2 Pu), 160.2 (C-6 Pu), 170.8 (C=O). IR (CHCl$_3$): 1739, 1590, 1500, 1456, 1406, 1383, 1364, 1332. HR-MS: calculated for C$_{18}$H$_{18}$N$_4$O$_2$ 322.1430, found 322.1416.

(E)-9-Benzyl-6-(buta-1,3-dien-1-yl)-9H-purine (**5**). M.p. 100–102 °C. ^{1}H NMR (CDCl$_3$, 500 MHz): 5.44 (s, 2 H, CH$_2$Ph); 5.46 (d, *J* = 10.2, 1 H, =CH=CH**H**$_{cis}$); 5.66 (d, *J* = 16.9, 1 H, =CH=CH**H**$_{trans}$); 6.66 (m, 1 H, C**H**=CH$_2$); 7.15 (d, *J* = 15.5, 1 H, Pu-C**H**=); 7.28–7.39 (m, 5 H, Ph); 8.01 (d, *J* = 15.3, 11.1, 1 H, Pu-CH=C**H**); 8.02 (s, 1 H, H-8 Pu); 8.91 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 47.2 (CH$_2$-Ph), 123.4 (=CH$_2$), 126.8 (Pu-CH=), 127.8 (CH Ph), 128.6 (CH Ph), 129.1 (CH Ph), 130.9 (C), 135.1 (C), 136.6 (**C**H=CH$_2$), 140.6 (Pu-CH=**C**H), 143.9 (H-8 Pu), 151.9 (C), 152.6 (C-2 Pu), 153.8 (C). IR (CHCl$_3$): 1635, 1606, 1583, 1498, 1453, 1403, 1328. HR-MS: calculated for C$_{16}$H$_{14}$N$_4$ 262.1218, found 262.1212.

Isomerization of Allylpurines 4a–4g

The solution of **4** (20 mg) and TsOH (1.2 mg) in THF was stirred at room temperature until the starting compound disappeared (2–78 h). The rearranged product was purified by chromatography on silica (10 g) in a hexane/ethyl acetate (2:1) mixture. In the case of **4a** the product crystallized from the reaction mixture, affording **6a** in 90% yield. The same reaction in homogenous solution in dichloromethane led to the equilibrium containing **4a** and **7a** in ca. 2:3 ratio.

9-Benzyl-6-(2-methylprop-1-en-1-yl)-9H-purine (**6a**). M.p. 136–138 °C (THF). ^{1}H NMR (CDCl$_3$, 300 MHz): 2.08 (d, *J* = 1.1, 3 H, CH$_3$); 2.38 (d, *J* = 1.1, 3 H, CH$_3$); 5.42 (s, 2 H, CH$_2$-Ph); 6.97 (s, 1 H, CH); 7.25–7.35 (m, 5 H, Ph); 7.97 (s, 1 H, H-8 Pu); 8.92 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 20.9 (CH$_3$), 28.2 (CH$_3$), 47.1 (CH$_2$-Ph), 117.8 (**C**H=C), 127.7 (CH Ph), 128.5 (CH Ph), 129.1 (CH Ph), 131.2 (C), 135.2 (C), 143.0 (C-8 Pu), 149.2 (CH=**C**), 151.2 (C), 152.2 (C-2 Pu), 155.8 (C). IR (CHCl$_3$): 2936, 1652, 1587, 1573, 1497, 1453, 1403, 1329. HR-MS: calculated for C$_{16}$H$_{16}$N$_4$ 264.1375, found 264.1373.

9-Benzyl-6-[(1E)-prop-1-en-1-yl]-9H-purine (**6b**). M.p. 89–92 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): 2.06 (dd, *J* = 6.9, 1.6, 3 H, CH$_3$); 2.08 (dd, *J* = 15.7, 1.6, 3 H, CH$_3$); 5.43 (s, 2 H, CH$_2$-Ph); 7.01 (td, *J* = 15.7, 1.6); 7.27–7.36 (m, 5 H, Ph); 7.63 (m, 1 H, =C**H**-CH$_3$); 7.99 (s, 1 H, H-8 Pu); 8.88 (s, 1 H, H-2 Pu). ^{13}C NMR (CDCl$_3$, 75 MHz): 19.2 (CH$_3$), 47.2 (CH$_2$-Ph), 126.6 (CH), 127.8 (CH), 128.5 (CH), 129.1 (CH), 130.3 (C), 135.2 (C), 140.2 (CH), 143.9 (C-8 Pu), 152.0 (C-2 Pu), 152.9 (C), 154.5 (C). IR (CHCl$_3$): 2992, 1659, 1588, 1499, 1455, 1405, 1329. HR-MS: calculated for C$_{15}$H$_{14}$N$_4$ 250.1218, found 250.1220.

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